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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,893	12/07/2006	Jo Klaveness	PN0398	7405
36335 7590 01/26/2012 GE HEALTHCARE, INC. IP DEPARTMENT 101 CARNEGIE CENTER PRINCETON, NJ 08540-6231				
EXAMINER SCHLIENTZ, LEAH H				
ART UNIT 1618		PAPER NUMBER		
NOTIFICATION DATE 01/26/2012		DELIVERY MODE ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

MDUSPatents@ge.com

Office Action Summary**Application No.**

10/582,893

Applicant(s)

KLAVENESS ET AL.

Examiner

Leah Schlientz

Art Unit

1618

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 October 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 1, 7, 8 and 11 is/are pending in the application.
- 5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 1, 7, 8 and 11 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-893)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____
- Paper No(s)/Mail Date ____

DETAILED ACTION

Status of Claims

Claim 1 has been amended. Claims 1, 7, 8 and 11 are pending and are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment. New grounds of rejection are set forth herein, necessitated by claim amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 7, 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeJesus *et al.* (*J. Label Compd. Radiopharm.*, 2003, 46, S1-S403, p. S1) in view of in view of Poss (US 2005/0214221), in further view of Kris *et al.* (*JAMA*, 2003, 290(16), p. 2149-2158).

DeJesus teaches that more than two thirds of human cancers derive from epithelial tissues and the EGFR-TK is overexpressed in the majority of these tumors. Numerous selective EGFR-TK inhibitors with nanomolar affinities have been developed as potential anti-cancer agents. One potent inhibitor that has progressed the furthest toward clinical registration is ZD1839 (or Iressa). ZD1839 is approved for clinical use in Japan and is close to obtaining U.S. FDA approval. ZD1839 is a fluorine-containing anilinoquinazoline which can be isotopically labelled with ^{18}F for use in clinical oncology as a PET imaging agent. Since extensive pre-clinical and clinical data on ZD1839 are available, the use of ^{18}F -ZD1839 to identify patients who would benefit from Iressa treatment and monitor its efficacy would be straightforward. We recently began the development of a reliable and efficient synthetic route for the routine preparation of ^{18}F -ZD1839. Initial biodistribution studies in normal HSD-ICR mice showed high uptake of ^{18}F -ZD1839 in the GI tract, liver, kidneys and bladder consistent with the known high EGFR localization in these organs. Plasma metabolite analysis in several mice up to 3 hr showed temporally decreasing percentage of unchanged ^{18}F -ZD1839 declining to 52% at 3 hr postinjection. Dynamic PET studies of mice using a Concorde microPET P4 scanner are underway (abstract).

Accordingly, DeJesus teaches ^{18}F radiolabeling of Iressa for PET imaging, but does not specifically teach providing a reporter detectable in optical imaging for optical imaging of lung cancer.

Poss teaches that nuclear imaging using various radiolabeled molecules has demonstrated some clinical utility in being able to image certain forms of molecular activity. Various radiolabeled metabolite imaging probes to image metabolic activity are known in the art and techniques of using these radiolabeled metabolite imaging probes to image metabolic activity are well established. Specifically, this technique has been used to successfully label and image several different metabolites including deoxyglucose. PET imaging using [^{18}F]fluorodeoxyglucose is well-established clinical cancer imaging method that can be used to detect very small tumors and monitor a patient's response to therapy (paragraph 0004). Although nuclear imaging of radioactively labeled metabolites has demonstrated some clinical utility, there remain significant limitations with these imaging approaches. Specifically, the short half-life of many radionuclides, including ^{18}F , ^{11}C , etc. severely limits the time available for synthesis and subsequent imaging, and therefore any facilities using these technologies require skilled radiochemists on staff to synthesize the imaging agents immediately prior to use. In the case of PET imaging, a cyclotron is usually required on-site because of the extremely short half-life of most positron-emitting radionuclides, including ^{18}F . In addition, clinical hardware systems required to detect positron and gamma emitting radionuclides are relatively expensive and therefore require a significant upfront capital investment. Because of these limitations, few clinical centers have the necessary

expertise, resources, and money to operate a nuclear imaging center effectively (paragraph 0005). Another significant disadvantage to nuclear imaging is that patients are exposed to radioactivity (paragraph 0006). Molecular optical imaging is a new imaging modality that generates molecular images using penetrating light rays. Preferably, light in the red and near infrared range (600-1200 nm) is used to maximize tissue penetration and minimize absorption from natural biological absorbers (paragraph 0007). There is a need for in vivo optical metabolite probes that are safer, less expensive and more convenient than current nuclear imaging probes (paragraph 0011). Optical imaging probes are disclosed having the formula $M_{(n)}-F$, where M is a metabolically recognizable molecule and F is a fluorochrome. Fluorochromes includes NIRFs having absorption and emission maximum between 600 and 1200 nm (paragraph 0021). Metabolically recognizable small drugs can be used, including drugs that are recognizable by tyrosine kinase (paragraph 0025). In vivo methods for optical imaging are also disclosed, including (a) administering to a subject an optical imaging probe (b) allowing time for the optical imaging probe to reach the target tissue and, preferably, but not necessary, for molecules in the target tissue to metabolize the probe; (c) illuminating the target tissue with light of a wavelength absorbable by the optical imaging probe; and (d) detecting the optical signal emitted by the optical imaging probe (paragraph 0032). The methods can be used in the detection, characterization and/or determination of the localization of a disease, especially early disease, including all types of cancer (paragraph 0038). Exemplary fluorochromes include Cy5.5, Cy5, Cy7, AlexaFluor, indocyanine green, etc (paragraph 0072).

Kris teaches that gefitinib (ZD1839, Iressa, AstraZeneca Pharmaceuticals, Wilmington, Del) blocks EGFR tyrosine kinases and prevents epidermal growth factor–induced proliferation in cell culture. It inhibits growth and causes regressions in human tumor xenografts with EGFR overexpression. In light of pre-clinical activity in EGFR-expressing tumors, evidence of EGFR expression in NSCLC, and antitumor effects in patients with NSCLC persisting after chemotherapy in the phase 1 trials, we initiated this phase 2 trial of gefitinib. We hypothesized that blocking EGFR tyrosine kinases with gefitinib would lead both to symptomatic benefits and objective regressions in patients with NSCLC (page 2150). Gefitinib, a well-tolerated oral EGFR-tyrosine kinase inhibitor, improved disease-related symptoms and induced radiographic tumor regressions in patients with NSCLC persisting after chemotherapy (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute a NIRF label for ^{18}F on ZD1830 (Iressa) inhibitors disclosed by DeJesus, and to perform optical imaging therewith when the teaching of DeJesus is taken in view of Poss. One would have been motivated to do so because Poss teaches that targeted optical imaging probes are superior to radiolabeled probes because of increased convenience (no need for on-site radiosynthesis), decreased cost, and increased safety (patients are not exposed to radioactivity). One would have had a reasonable expectation of success in doing so because both DeJesus and Poss are directed to molecular imaging methods, and because Poss teaches that a variety of targeting moieties can be conjugated to fluorochromes, including drugs that are recognizable by tyrosine kinase. While DeJesus teaches that a variety of human

cancers derive from epithelial tissues and the EGFR-TK is overexpressed in the majority of these tumors, it is not specifically recited that imaging of lung cancer is performed. However, it is known in the art that there is evidence of EGFR expression in NSCLC and that Gefitinib (ZD1830, Iressa) improved disease-related symptoms and induced radiographic tumor regressions in patients with NSCLC, as shown by Kris. Accordingly, one of ordinary skill performing optical imaging using EGFR-TK inhibitor probes would have a reasonable expectation that such probes would distribute to lung cancer. Optical imaging using targeted fluorochrome probes can be used in the detection, characterization and/or determination of the localization of a disease, including cancer, as shown by Poss.

Double Patenting

Claims 1, 7, 8 and 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7 and 8 of copending Application No. 10/582,679 in view of US 2006/0067947. Both sets of claims are drawn to methods of optical imaging comprising administering an optical imaging contrast agent having overlapping chemical structures V-L-R. While the instant claims recite imaging of lung cancer and the claims of the '679 application recite imaging of oesophageal cancer, it would have been obvious to one of ordinary skill in the art at the time of the invention to provide V-L-R for imaging lung cancer or esophageal cancer when the claims are taken in view of US 2006/0067947 which shows that Iressa (corresponding to variable R in both applications) may treat either lung cancer or

esophageal cancer, among others (paragraph 0099). Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Wednesday 9 AM-5 PM and telework Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LHS/
/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618